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TITLE: Method of inhibiting angiogenesis of tumors

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CLAIMS:

We claim:

1. A method of inhibiting angiogenesis in a human patient, comprising administering to the patient a vascularization inhibitor comprising substantially pure human thrombospondin in trimer or monomer form, or a substantially pure fragment thereof capable of inhibiting vascularization.

2. The method of claim 1 in which said thrombospondin is in trimer glycosylated form.

3. The method of claim 1 in which said thrombospondin is in monomer glycosylated form.

4. The method of claim 1 in which said inhibitor corresponds essentially with a glycosylated trimer composed of the approximately 140 kilodalton (kD) fragments obtainable by enzymatic digestion of natural human thrombospondin, said fragments not containing a heparin binding domain associated with the amino end portion of the natural thrombospondin monomer.

5. The method of claim 1 in which said inhibitor corresponds essentially with a glycosylated trimer composed of the approximately 120 kilodalton (kD) fragments obtainable by enzymatic digestion of human thrombospondin, said fragments not containing either the heparin binding domain associated with the amino end portion of the thrombospondin monomer or the platelet binding domain associated with the carboxyl end portion of the thrombospondin monomer.

6. The method of claim 1 in which said inhibitor is a monomer corresponding essentially with the 140 kilodalton (kD) fragments obtainable by enzymatic digestion of human thrombospondin, said fragments not containing a heparin binding domain associated with the amino end portion of the thrombospondin monomer.

7. The method of claim 1 in which said inhibitor corresponds essentially with a glycosylated monomer composed of the approximately 120 kilodalton (kD) fragments obtainable by enzymatic digestion of human thrombospondin, said fragments not

containing either the heparin binding domain associated with the amino end portion of the thrombospondin monomer or the platelet binding domain associated with the carboxyl end portion of the thrombospondin monomer.

8. The method of claim 1 in which said inhibitor corresponds with the approximately 70 kD monomer fragments obtainable by enzymatic digestion of the 120 kD monomer fragments, of human thrombospondin, said 70 kD fragments not containing a fibrogen binding domain associated with the carboxyl end portion of said 120 kD monomer.

9. The method of claim 1 in which the patient is being treated for an internal tumor, and said inhibitor before administration is admixed with a slow release agent and thereafter a portion of the mixture is implanted in the tumor.

10. The method of claim 1 in which the tumor being treated is a skin cancer and said inhibitor before administration is admixed with a topical vehicle and thereafter applied to the surface of the skin cancer.

11. The method of claim 1 in which said inhibitor corresponds with a fragment of the human thrombospondin trimer which contains a region capable of inhibiting angiogenesis as determined by the rat corneal assay, said fragment being in trimer or monomer form, and said trimer and monomer forms being either glycosylated or non-glycosylated.

12. The method of claim 11 in which said fragment is in a glycosylated form.

13. In the treatment of human patients having growing solid tumors with associated neovascularization, the method of retarding tumors growth comprising administering to the site of the patient's tumor a vascularization inhibitor comprising substantially pure human thrombospondin in trimer or monomer form, or substantially pure fragments thereof capable of inhibiting vascularization, said inhibitor being applied to the tumor in an amount effective for retarding its enlargement.

14. The method of claim 13 in which said inhibitor corresponds with a fragment of the human thrombospondin trimer which contains a region capable of inhibiting angiogenesis as determined by the rat corneal assay, said fragment being in trimer or monomer form, and said trimer and monomer forms being either glycosylated or non-glycosylated.

15. A therapeutic product for controlling angiogenesis, comprising implantable pellets composed essentially of a slow release agent in admixture with a vascularization inhibitor comprising substantially pure human thrombospondin in trimer or monomer form, or substantially pure fragmented thereof capable of inhibiting vascularization.

16. A therapeutic product for controlling angiogenesis, comprising a topical vehicle in admixture with a vascularization inhibitor comprising substantially pure human thrombospondin in trimer or monomer form, or substantially pure fragments thereof capable of inhibiting vascularization.

17. The therapeutic preparations of claims 15 or 16 in which thrombospondin is in its trimer glycosylated form.

18. The therapeutic preparations of claims 15 or 16 in which said thrombospondin is in monomer glycosylated form.

19. The therapeutic preparations of claims 15 or 16 in which said inhibitor corresponds essentially with a glycosylated trimer composed of the approximately 140 kilodalton (kD) fragments obtainable by enzymatic digestion of human thrombospondin, said fragments not containing a heparin binding domain associated with the amino end portion of the natural thrombospondin monomer.

20. The therapeutic preparations of claims 15 or 16 in which said inhibitor corresponds essentially with a glycosylated trimer composed of the approximately

120 kilodalton (kD) fragments obtainable by enzymatic digestion of human thrombospondin, said fragments not containing either the heparin binding domain associated with the amino end portion of the thrombospondin monomer or the platelet binding domain associated with the carboxyl end portion of the thrombospondin monomer.

21. The therapeutic preparations of claims 15 or 16 in which said inhibitor is a monomer corresponding essentially with the 140 kilodalton (kD) fragments obtainable by enzymatic digestion of human thrombospondin, said fragments not containing a heparin binding domain associated with the amino end portion of the thrombospondin monomer.

22. The therapeutic preparations of claims 15 or 16 in which said inhibitor corresponds essentially with a glycosylated trimer composed of the approximately 120 kilodalton (kD) fragments obtainable by enzymatic digestion of human thrombospondin, said fragments not containing either the heparin binding domain associated with the amino end portion of the thrombospondin monomer or the platelet binding domain associated with the carboxyl end portion of the thrombospondin monomer.

23. The therapeutic preparations of claims 15 or 16 in which said inhibitor corresponds with the approximately 70 kD monomer fragments obtainable by enzymatic digestion of the 120 kD monomer fragments of human thrombospondin, said 70 kD fragments not containing a fibrogen binding domain associated with the carboxyl end portion of the 120 kD monomer.

24. The therapeutic preparations of claims 15 or 16 in which said inhibitor corresponds with a fragment of the human thrombospondin trimer which contains a region capable of inhibiting angiogenesis as determined by the rat corneal assay, said fragment being in trimer or monomer form, and said trimer and monomer forms being either glycosylated or non-glycosylated.